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NOVOZYMES NORTH AMERICA, INC.
500 FIFTH AVENUE
SUITE 1600
NEW YORK, NY 10110

EXAMINER	
COLLINS, CYNTHIA E	
ART UNIT	**PAPER NUMBER**
1638	

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/981,009	KJAERULFF ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,15,19,23-27 and 32* is/are pending in the application.

4a) Of the above claim(s) *27 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,15,19 and 23-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Amendment

Claims 13, 14, 16-18, 20-22, 28-31 and 33-34 were cancelled without prejudice or disclaimer in the preliminary amendment filed October 16, 2001.

Claims 1-12, 15, 19, 23-27 and 32 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, e.g. claims 1-26, in the reply filed on October 24, 2003 is acknowledged. The traversal is on the ground(s) that examination of the claims of Groups I and II would not be a serious burden. Applicant also submits that claim 1 links the inventions of Groups I and II, and requests that upon allowance of the linking claim the restriction requirement as to the linked inventions should be withdrawn.

This is not found persuasive because claim 1 does not link the inventions of Groups I and II. The transgenic plant of Group II is not made by the method of claim 1. Furthermore, the transgenic plant of Group II is transformed with a nucleotide sequence encoding a protein allergen having modified immunogenicity, whereas the transgenic plant prepared by the method of claim 1 is transformed with a nucleotide sequence encoding an unspecified protein variant having modified immunogenicity. Accordingly, claim 1 does not link the inventions of Groups I and II. This is also not found persuasive because the invention of Group II requires a separate search for a transgenic plant transformed with a nucleotide sequence encoding a protein allergen having modified immunogenicity. Accordingly, claims 27 and 32, directed to the inventions of Groups II

and III, are withdrawn from consideration as being directed to nonelected inventions. Claims 1-12, 15, 19 and 23-26, directed to the elected invention of Group I, are examined.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

Claim 12 is objected to because of the following informalities: claim 12 refers to the method of "claims" 9; "claims" and 9 do not agree in number. Appropriate correction is required.

Claim 12 is objected to because of the following informalities: claim 12 recites "an amino acid which render": "amino acid" and "render" do not agree in number. Appropriate correction is required.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, filed April 4, 2002 is attached to the instant Office action.

Claim Rejections - 35 USC § 112

Claims 1-12, 15, 19 and 23-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of preparing a transgenic plant expressing a protein variant having modified immunogenicity, including reduced allergenicity, as compared to a parent protein, including an environmental allergen or food allergen, comprising the steps of: (a) obtaining antibody binding peptide sequences involved in antibody binding, (b) using the sequences to localize epitope sequences on the primary and/or the 3-dimensional structure of any unspecified parent protein obtained from any unspecified source, (c) defining an epitope area including amino acids situated within 5A from the epitope amino acids constituting the epitope sequence, (d) changing one or more of the amino acids defining the epitope area of the parent protein by genetic engineering mutations of a DNA sequence encoding the parent protein, including changing by substituting, adding and/or deleting at least one unspecified amino acid and including changing by substituting and/or inserting at least one amino acid which is a target for in vivo posttranslational modification, including substituting and/or inserting the amino acids K, C, D, E, Q, R and Y, (e) introducing the mutated DNA sequence into a suitable host, culturing the host and expressing the protein variant, (f) evaluating the immunogenicity of the protein variant using the parent protein as reference, (g) introducing the mutated DNA sequence into an expression construct and transforming a suitable plant cell with the construct, and (h) regenerating the plant from the plant cell.

The specification describes the location of epitope sequences and epitope areas on a single parent protein, the major birch pollen allergen Bet v1 (page 69 Table 1; page 71 lines 24-26; page 72 lines 5-18). The specification does not describe the structural features of Bet v1 protein variants that have modified immunogenicity or reduced allergenicity as a consequence of one or more changes in one or more of the amino acids

defining the Bet v1 epitope area. The specification also does not describe other parent proteins, their epitope sequences and epitope areas, or the structural features of protein variants thereof that have modified immunogenicity or reduced allergenicity as a consequence of one or more changes in one or more of the amino acids defining the their epitope areas.

The Federal Circuit has recently clarified the application of the written description requirement. The court stated that "A description of a genus of cDNAs may be achieved by means of recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." See *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In the instant case Applicant has not described a representative number of species falling within the scope of the claimed genus which encompasses coding sequences for variants of any protein obtained from any source in which one or more unspecified changes has been made in an undisclosed epitope area. Applicant also has not described the specific structural features unique to the genus that are correlated with the modified immunogenicity or reduced allergenicity characteristic of the variant species.

Claims 1-12, 15, 19 and 23-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification discloses the location of epitope sequences and epitope areas on a single parent protein, the major birch pollen allergen Bet v1 (page 69 Table 1; page 71 lines 24-26; page 72 lines 5-18). The specification does not disclose Bet v1 protein variants that have modified immunogenicity or reduced allergenicity as a consequence of one or more changes in one or more of the amino acids defining the Bet v1 epitope area. The specification also does not disclose the location of epitope sequences and epitope areas other parent proteins, or protein variants thereof that have modified immunogenicity or reduced allergenicity as a consequence of one or more changes in one or more of the amino acids defining the their epitope areas.

The claimed invention is not enabled because the effect of making one or more changes in one or more of the amino acids defining the epitope area of a protein on the immunogenicity or allergenicity of that protein is unpredictable. It is unpredictable because the epitope areas of different proteins comprise different amino acid sequences, and because each epitope area is unique with respect to the specific type and specific location of amino acid changes that would cause the epitope area to confer modified immunogenicity or reduced allergenicity to a protein variant.

See, for example, Schramm et al. (The Journal of Immunology, 1999, Volume 162, pages 2406-2414), who teach that timothy grass pollen allergen Phl p 5b protein variants having point mutations in the in the IgE binding region epitope (PM1 having two point mutations $D^{49} \rightarrow L$ and $K^{50} \rightarrow A$, and PM3 having one point mutation $A^{13} \rightarrow C$), did not show any significant reduction of IgE reactivity, whereas timothy grass pollen

allergen Phl p 5b protein variants having deletions showed significant reduction of IgE reactivity (page 408 Figure 1; page 2409 Table I and paragraph spanning column 1 and 2; page 2410 Table II and Figures 3 and 4; page 2411 Figure 5 Table III; page 2412 Tables IV and V). Schramm et al. also teach that while their PM1 point mutations were targeted to the putative N-terminal continuous IgE-binding epitope and expected to clearly reduce IgE reactivity, the failure of PM1 to clearly reduce IgE reactivity could possibly be attributed to amino acid exchanges inappropriate for elimination of the targeted IgE-binding epitope and/or the presence of multiple IgE-binding epitopes in the variant (page 2412 column 2 to page 2413 column 3 first paragraph).

See also, for example, Neudecker et al. (Biochem. J. 2003, Vol 376, pages 97-107), who teach protein variants having point mutations in the in the IgE epitope containing P-loop region of cherry major allergen Pru av 1and celery major allergen Api g 1. Neudecker et al. teach that mutation in Pru av 1 of $Glu^{45} \rightarrow$ Trp reduced IgE reactivity, mutation in Pru av 1 of $Ser^{112} \rightarrow$ Pro resulted in an almost complete loss of IgE reactivity, and mutation in Api g 1 of $Lys^{44} \rightarrow$ Glu enhanced IgE reactivity, whereas neither the mutation in Pru av 1 of $Ser^{112} \rightarrow$ Ala nor the deletion in Pru av 1 of amino acids 155-159, affected IgE reactivity (page 97 abstract; page 99 Table 1; page 102 Figures 3 and 4).

In the instant case Applicant has not provided guidance with respect to where and how to specifically change the amino acids defining the epitope area of any parent protein such that the resultant protein variant exhibits modified immunogenicity or reduced allergenicity. Absent such guidance one skilled in the art would have to make and test each type and configuration of change (substitutions, additions and/or deletions) in the

amino acids defining the epitope area(s) of each parent protein in order to discriminate between those protein variants that would be useful for preparing a transgenic plant expressing a protein variant having modified immunogenicity as compared to a parent protein and those that would not. Such a trial and error experimental approach would constitute undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 27 and 32, and claims 2-12, 15 and 23-26 dependent thereon, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 27 and 32 are indefinite in the recitation of "modified immunogenicity". It is unclear in what way immunogenicity is modified, since immunogenicity may be modified in different ways to different ends.

Claim 1, and claims 2-12, 15, 19 and 23-26 dependent thereon, are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Part (a) of claim 1 requires obtaining antibody binding peptide sequences involved in antibody binding, but claim 1 does not specify how this may be accomplished. Part (b) of claim 1 requires using the antibody binding peptide sequences involved in antibody binding obtained in part (a) to localize epitope sequences on the primary and/or the 3-dimensional structure of a parent protein, but claim 1 does not specify how this may be accomplished. Part (c) of claim 1 requires defining an epitope area including amino acids situated within 5A

from the epitope amino acids constituting the epitope sequence, but claim 1 does not specify how this may be accomplished. Part (f) of claim 1 requires evaluating the immunogenicity of the protein variant using the parent protein as reference, but claim 1 does not specify how this may be accomplished.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 recites the limitation "the protein allergen" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6 provides for the identification of epitope patterns by sequence alignment in the method of claim 1, but it is unclear at what point in method 1 the identification step would occur.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 8 requires the identification of hot spot amino acids in the method of claim 1, but claim 8 does not specify how this may be accomplished.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 8 provides for the identification of hot spot amino acids in the method of claim 1, but it is unclear at what point in method 1 the identification step would occur.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 10 provides for changing the epitope sequence in the method of claim 1, but it is unclear at what point in method 1 the step for changing the epitope sequence would occur.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 11 recites the limitation "the hot spot amino acids" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 12 is indefinite in the recitation of " a target for in vivo posttranslational modification". It is unclear what type of in vivo posttranslational modification the amino acid would be a target for, as different amino acids may be the target for different types of in vivo posttranslational modification, and the amino acid target is not specified.

Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 19 is indefinite in the recitation of " reduced", as "reduced" is a relative term that lacks a comparative basis.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 23 is indefinite in the recitation of " environmental". It is

unclear how an environmental allergen would be distinguished from other allergens, as all allergens find their origin in some type of environment.

Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25 recites the limitation "the host cell" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7-11, 19 and 23-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Sosin et al. (WO 99/38978 published 5 August 1999, Applicant's IDS).

The claims are drawn to a method of preparing a transgenic plant expressing a protein variant having reduced allergenicity, as compared to a food allergen parent protein comprising the steps of: (a) obtaining antibody binding peptide sequences involved in antibody binding by screening a library of known peptides related to the primary sequence of the parent protein with antibodies raised against a protein allergen, including by screening a random phage peptide display package library, (b) using the sequences to localize epitope sequences on the primary structure of the parent protein, (c) defining an epitope area including amino acids situated within 5Å from the epitope amino acids constituting the epitope sequence, (d) changing one or more of the amino acids

defining the epitope area of the parent protein by genetic engineering mutations of a DNA sequence encoding the parent protein, including changing by substituting, adding and/or deleting at least one amino acid, (e) introducing the mutated DNA sequence into a suitable bacterial host, culturing the host and expressing the protein variant, (f) evaluating the immunogenicity of the protein variant using the parent protein as reference, (g) introducing the mutated DNA sequence into an expression construct and transforming a suitable plant cell with the construct, and (h) regenerating the plant from the plant cell. The claims also require the identification of hot spot amino acids of the parent protein.

Sosin et al. teach a method of preparing a transgenic plant expressing a protein variant having reduced allergenicity as compared to the major peanut food allergen parent proteins Ara h 1, Ara h 2 and Ara h 3 comprising the steps of: (a) obtaining antibody binding peptide sequences involved in antibody binding by screening a library of known peptides related to the primary sequence of the parent proteins with IgE antibodies obtained from patients with documented peanut hypersensitivity reactions (page 15 line 17 to page 16 line 5; page 17 line 25 to page 18 line 2), including by screening a random phage peptide display package library (page 7 line 32 to page 8 line 3), (b) using the sequences to localize epitope sequences on the primary structure of the parent proteins (page 18 line 3 through page 20), (c) defining a linear epitope area including amino acids situated within 5Å from the epitope amino acids constituting the epitope sequence (page 18 line 3 through page 20; sequence listing SEQ ID NOS:2, 4, and 6), (d) changing one or more of the amino acids defining the epitope area of the parent protein by genetic engineering mutations of a DNA sequence encoding the parent protein, (page 21 line 10 through page 24; page 25 lines 3-5), (e) introducing the mutated DNA sequence into a

suitable bacterial host, culturing the host and expressing the protein variant (page 16 line 22 to page 17 line 9; page 25 lines 3-6), (f) evaluating the immunogenicity of the protein variant using the parent protein as reference (page 17 lines 10-23; page 25 line 10 through page 26), (g) introducing the mutated DNA sequence into an expression construct and transforming a suitable plant cell with the construct (page 10 lines 17-30), and (h) regenerating the plant from the plant cell (page 10 lines 17-30). Sosin et al. also identify the amino acids at positions 144, 145, 147 and 148 of Ara h 1 as hot spot amino acids (page 21 lines 23-26).

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Cynthia Collins Cynthia Collins 8/19/04